

WHAT IS CLAIMED IS:

1. A method of determining a consensus profile for a particular biological response, said method comprising identifying common response motifs among sets of co-varying cellular constituents in a plurality of response profiles, wherein said common response motifs are associated with the particular biological response.

2. The method of claim 1, wherein the plurality of response profiles comprises at least five response profiles.

3. The method of claim 2, wherein the plurality of response profiles comprises more than ten response profiles.

4. The method of claim 3, wherein the plurality of response profiles comprises more than 50 response profiles.

5. The method of claim 4, wherein the plurality of response profile comprises more than 100 response profiles.

6. The method of claim 1, wherein the particular biological response is a biological response associated with a particular biological effect.

7. The method of claim 6, wherein the particular biological effect is the effect of a particular class or type of drug.

8. The method of claim 6, wherein the particular biological effect is a therapeutic effect.

9. The method of claim 6, wherein the particular biological effect is a toxic effect.

10. The method of claim 1, wherein the sets of co-varying cellular constituents comprise cellular constituents which are co-regulated.

11. The method of claim 1, wherein the sets of co-varying cellular constituents comprise cellular constituents which co-vary in the plurality of response profiles.
12. The method of claim 11, wherein the cellular constituents which co-vary are
5 identified by cluster analysis of cellular constituents in the plurality of response profiles.
13. The method of claim 12, wherein the cluster analysis is done by means of a clustering algorithm.
- 10 14. The method of claim 13, wherein the clustering algorithm is *hclust*.
15. The method of claim 12, wherein said cluster analysis determines a clustering tree, the cellular constituents which co-vary comprising branches of said clustering tree.
- 15 16. The method of claim 15, wherein the sets of co-varying cellular constituents are selected from a branching level of the clustering tree.
17. The method of claim 12, wherein a statistical significance for the sets of co-varying cellular constituents is determined by means of an objective statistical test.
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18. The method of claim 17, wherein the objective statistical test comprises:
- (a) determining an actual fractional improvement in cluster analysis of the cellular constituents;
 - (b) generating permuted cellular constituents by means of Monte Carlo
25 randomization of each response profile for each cellular constituent;
 - (c) performing cluster analysis on the permuted cellular constituents;
 - (d) determining the fractional improvement in the cluster analysis on the permuted cellular constituents; and
 - (e) repeating said steps of generating permuted cellular constituents and
30 performing cluster analysis on the permuted cellular constituents so that a distribution of fractional improvements is obtained,

wherein the statistical significance is determined by comparing the actual fractional improvement to the distribution of fractional improvements.

19. The method of claim 1, wherein the common response motifs are identified by re-ordering the response profiles into sets associated with similar biological effects.
20. The method of claim 19, wherein the sets of response profiles associated with similar biological effects are identified by cluster analysis of the response profiles.
21. The method of claim 20, wherein the cluster analysis is done by means of a clustering algorithm.
22. The method of claim 21, wherein the clustering algorithm is *hclust*.
23. The method of claim 20, wherein said cluster analysis determines a clustering tree, the cellular constituents which co-vary comprising branches of said clustering tree.
24. The method of claim 23, wherein the branches are selected by applying a cutting level across said clustering tree, said cutting level being determined by an expected number of biological pathways represented by the cellular constituents which co-vary.
25. The method of claim 20, wherein a statistical significance for the sets of co-varying cellular constituents is determined by means of an objective statistical test.
26. The method of claim 25, wherein the objective statistical test comprises:
- (a) determining an actual fractional improvement in the cluster analysis of the response profiles
 - (b) generating permuted response profiles by means of Monte Carlo randomization of each response profile;
 - (c) performing cluster analysis on the permuted response profiles;
 - (d) determining the fractional improvement in the cluster analysis on the permuted response profiles; and

(e) repeating said steps of generating permuted response profiles and performing cluster analysis on the permuted response profiles so that a distribution of fractional improvements is obtained, wherein the statistical significance is determined by comparing the actual fractional improvement to the distribution of fractional improvements.

27. The method of claim 1, wherein the sets of co-varying cellular constituents comprise basis cellular constituent sets.

28. The method of claim 27, wherein the basis cellular constituent sets are genesets.

29. The method of claim 27, further comprising prior to said identifying the step of converting the response profiles into projected response profiles by means of projecting the response profile onto the basis cellular constituent sets, wherein said projected response profiles are the response profiles of said identified common response motifs.

30. The method of claim 1 wherein the consensus profile is the intersection of the sets of co-varying cellular constituents activated or de-activated in the common response motifs.

31. The method of claims 30, wherein the sets of co-varying cellular constituents comprise basis cellular constituent sets, and further comprising prior to said identifying the step of converting the response profiles into projected response profiles by means of projecting the response profiles onto the basis cellular constituent sets, wherein said projected response profiles are the response profiles of said identified common response motifs.

32. The method of claim 30 or 31, wherein the common response motifs are identified by re-ordering the response profiles into sets associated with similar biological effects.

33. The method of claim 31, wherein the intersection is identified by visual inspection of the plurality of projected response profiles.

34. The method of claim 32, wherein the intersection is identified by visual inspection of the plurality of projected response profiles.

35. The method of claim 31, wherein the intersection is identified by thresholding the
5 projected response profiles.

36. The method of claim 31, wherein the intersection is identified arithmetically.

37. The method of claim 36, wherein the intersection is identified by a method
10 comprising:

- (a) replacing amplitudes of cellular constituent sets in the projected response profiles that are above a threshold with values of unity;
- (b) replacing amplitudes of cellular constituent sets in the projected response profiles that are below said threshold with values of zero; and
- 15 (c) determining the element-wise product of the projected response profiles, wherein the element-wise product of the projected response profiles is the intersection.

38. A method of determining a consensus profile for a particular biological response, said method comprising identifying common response motifs among sets of co-varying
20 genesets in a plurality of response profiles, said response profiles comprising expression profiles of a plurality of genes, wherein said common response motifs are associated with the particular biological response.

39. A method for comparing a biological response profile to a consensus profile
25 provided by identifying common response motifs among sets of co-varying cellular constituents in a plurality of response profile which are associated with a particular biological response, said method comprising:

- 30 (a) converting the biological response profile into a projected response profile according to a definition of basis cellular constituent sets, wherein each of said basis cellular constituent sets comprises cellular constituents which co-vary in the plurality of response profiles; and

- (b) determining the value of a similarity metric between the projected response profile and the consensus profile.

40. The method of claim 39, wherein said step of converting comprising projecting the
5 biological response profile onto the basis cellular constituent sets.

41. The method of claim 39, wherein the similarity metric is the generalized cosine angle between the projected response profile and the consensus profile.

10 42. The method of claim 39, further comprising a step of determining the statistical significance of the similarity metric.

43. The method of claim 42, wherein the statistical significance is assessed using an empirical probability of distribution generated under a null hypothesis of no correlation.
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44. A method for grouping measured response profiles in sets which are associated with similar biological effects comprising identifying sets of response profiles based upon
15 similar responses of a plurality of cellular constituents in the response profiles.

20 45. The method of claim 44, wherein the sets of response profiles are identified by cluster analysis of the response profiles.

46. The method of claim 45, wherein the cluster analysis is done by means of a clustering algorithm.
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47. The method of claim 45, wherein the clustering algorithm is *hclust*.

48. The method of claim 45, wherein said cluster analysis determines a clustering tree, the sets of response profiles comprising branches of said clustering tree.
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49. The method of claim 45, wherein a statistical significance for the sets of response profiles is determined by means of an objective statistical test.

50. The method of claim 49, wherein the objective statistical test comprises:
- (a) determining an actual fractional improvement in the cluster analysis of the response profiles;
 - (b) generating permuted response profiles by means of Monte Carlo randomization of cellular constituents for each response profile;
 - (c) performing cluster analysis on the permuted response profiles;
 - (d) determining the fractional improvement in the cluster analysis of the permuted response profiles; and
 - (e) repeating said steps of generating permuted response profiles and performing cluster analysis on the permuted response profiles so that a distribution of fractional improvements is obtained,
- wherein the statistical significance is determined by comparing the actual fractional improvement to the distribution of fractional improvements.
51. A method for classifying a drug or drug candidate comprising identifying sets of response profiles having similar responses of a plurality of cellular constituents to one or more measured response profiles associated with exposure to the drug or drug candidate, wherein each of said sets corresponds to a particular class of drug or drug candidate, and wherein the drug or drug candidate is classified according to the identified sets.
52. The method of claim 51, wherein the sets of response profiles are identified by cluster analysis of the response profiles.
53. The method of claim 52, wherein the cluster analysis is done by means of a clustering algorithm.
54. The method of claim 53, wherein the clustering algorithm is *hclust*.
55. The method of claim 52, wherein said cluster analysis determines a clustering tree, the sets of response profiles comprising branches of said clustering tree.

56. The method of claim 52, wherein a statistical significance for the sets of response profiles is determined by means of an objective statistical test.

57. The method of claim 56, wherein the objective statistical test comprises:

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- (a) determining an actual fractional improvement in the cluster analysis of the response profiles;
 - (b) generating permuted response profiles by means of Monte Carlo randomization of cellular constituents for each response profile;
 - (c) performing cluster analysis on the permuted response profiles;
 - 10 (d) determining the fractional improvement in the cluster analysis of the permuted response profiles; and
 - (e) repeating said steps of generating permuted response profiles and performing cluster analysis on the permuted response profiles so that a distribution of fractional improvements is obtained,

15 wherein the statistical significance is determined by comparing the actual fractional improvement to the distribution of fractional improvements.

58. A method for determining the therapeutic efficacy of a drug or drug candidate comprising identifying sets of response profiles having similar responses of a plurality of
20 cellular constituents to one or more measured response profiles associated with exposure to the drug or drug candidate, wherein each of said sets corresponds to a particular therapeutic effect, and wherein the therapeutic efficacy of the drug or drug candidate is determined according to the identified sets.

25 59. The method of claim 58, wherein the sets of response profiles are identified by cluster analysis of the response profiles.

60. The method of claim 59, wherein the cluster analysis is done by means of a clustering algorithm.

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61. The method of claim 60, wherein the clustering algorithm is *hclust*.

62. The method of claim 59, wherein said cluster analysis determines a clustering tree, the sets of response profiles comprising branches of said clustering tree.

63. The method of claim 59, wherein a statistical significance for the sets of response
5 profiles is determined by means of an objective statistical test.

64. The method of claim 63, wherein the objective statistical test comprises:

- (a) determining an actual fractional improvement in the cluster analysis of the response profiles;
- 10 (b) generating permuted response profiles by means of Monte Carlo randomization of cellular constituents for each response profile;
- (c) performing cluster analysis on the permuted response profiles;
- (d) determining the fractional improvement in the cluster analysis of the permuted response profiles; and
- 15 (e) repeating said steps of generating permuted response profiles and performing cluster analysis on the permuted response profiles so that a distribution of fractional improvements is obtained,

wherein the statistical significance is determined by comparing the actual fractional improvement to the distribution of fractional improvements.

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65. A method for determining the toxicity of a drug or drug candidate comprising identifying sets of response profiles having similar responses of a plurality of cellular constituents to one or more measured response profiles associated with exposure to the drug or drug candidate, wherein each of said sets corresponds to a particular toxic
25 effect, and wherein the toxicity of the drug or drug candidate is determined according to the identified sets.

66. The method of claim 65, wherein the sets of response profiles are identified by cluster analysis of the response profiles.

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67. The method of claim 66, wherein the cluster analysis is done by means of a clustering algorithm.

68. The method of claim 67, wherein the clustering algorithm is *hclust*.
69. The method of claim 66, wherein said cluster analysis determines a clustering tree, the sets of response profiles comprising branches of said clustering tree.
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70. The method of claim 66, wherein a statistical significance for the sets of response profiles is determined by means of an objective statistical test.
71. The method of claim 70, wherein the objective statistical test comprises:
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- (a) determining an actual fractional improvement in the cluster analysis of the response profiles;
 - (b) generating permuted response profiles by means of Monte Carlo randomization of cellular constituents for each response profile;
 - (c) performing cluster analysis on the permuted response profiles;
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 - (d) determining the fractional improvement in the cluster analysis of the permuted response profiles; and
 - (e) repeating said steps of generating permuted response profiles and performing cluster analysis on the permuted response profiles so that a distribution of fractional improvements is obtained,
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- wherein the statistical significance is determined by comparing the actual fractional improvement to the distribution of fractional improvements.
72. A method for analyzing a biological sample comprising
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- (a) grouping cellular constituents from the biological sample into sets of cellular constituents that co-vary in response profiles obtained from the biological sample; and
 - (b) grouping the biological profiles obtained from the biological sample into sets of biological profiles that effect similar cellular constituents.
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73. The method of claim 72, wherein one or more cellular constituents which co-vary in association with a particular biological effect are identified from the sets of cellular constituents that co-vary in biological profiles.

74. The method of claim 72, wherein one or more response profiles that are associated with a particular biological effect are identified from the sets of biological profiles that affect similar cellular constituents.

5 75. The method of claim 73 or 74, wherein the particular biological effect is a biological pathway.

76. The method of claim 73, wherein the cellular constituents from the biological sample comprise a plurality of genes or gene transcripts, and one or more genes associated
10 with a particular biological effect are identified.

77. The method of claim 76 wherein the one or more genes identified comprise known genes.

15 78. The method of claim 76, wherein the one or more genes identified comprise previously unknown genes.

79. A computer system comprising a computer-usable medium having computer readable program code embodied thereon for effecting the following steps within said
20 computer system:

- (a) receiving data from a plurality of response profiles;
- (b) receiving a definition for cellular constituent sets;
- (c) identifying common response motifs among the cellular constituent sets in the plurality of response profiles,

25 wherein said common response motifs comprise consensus profiles.

80. The computer system of claim 79, further comprising computer readable program code embodied thereon for effecting within said computer system the step of calculating projected profiles based upon the received definition of cellular constituent sets and one or
30 more of said response profiles.

81. The computer system of claim 79, further comprising computer readable program code embodied thereon for effecting within said computer system the steps of:

- (i) receiving criteria for the selection of cellular constituent sets;
- (ii) clustering the received response data; and
- 5 (iii) defining cellular constituent sets based upon said clustered response data and said criteria for the selection of cellular constituent sets,

wherein said step of receiving a definition for cellular constituent sets comprises said steps of receiving criteria, clustering, and defining cellular constituent sets.

10 82. The computer system of claim 79, 80, or 81, wherein the data from the plurality of response profiles is entered directly by a user.

83. The computer system of claim 79, 80, or 81, wherein the data from the plurality of response profiles is loaded from a mass storage means.

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84. The computer system of claim 79, 80, or 81, wherein the data from the plurality of response profiles is loaded from a removable storage means.

85. The computer system of claim 79 or 80, wherein said definition for cellular
20 constituent sets is entered directly by a user.

86. The computer system of claim 79 or 80, wherein said definition for cellular constituent sets is received from a dynamic database system of cellular constituent sets.

25 87. A computer system comprising computer readable program code embodied thereon for effecting within said computer system the steps of:

- (a) receiving a projected response profile;
- (b) receiving a consensus profile; and
- 30 (c) calculating the similarity between the projected response profile and the consensus profile.

88. The computer system of claim 87, wherein the step of receiving a consensus profile comprises:

- (i) receiving data from a plurality of response profiles;
- (ii) receiving a definition for cellular constituent sets;
- 5 (iii) identifying common response motifs among the cellular constituent sets in the plurality of response profiles.

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